Metabolic Syndrome Across the Life Cycle - Adolescent

Joy Friedman MD
Disclosures

• I have no actual or potential conflict of interest in relation to this program or presentation.
• I will mention off-label use of Metformin for pediatric obesity and polycystic ovarian syndrome.
Objectives

• Review definitions of Pediatric Metabolic Syndrome in the literature

• Identify common comorbid conditions

• Discuss weight-related talk in relationship to disordered eating patterns which may interfere with management of obesity

• Support age appropriate culturally sensitive strategies for addressing obesity in the adolescent patient
Percentage of high school students who had obesity, *2015†

CDC YRBS 2015
Defining Metabolic Syndrome: Cardiovascular risk

- Elevated triglyceride levels and reduced high-density lipoprotein (HDL)
  - Lipid levels vary by age, sexual maturity stage, sex and race
- Elevated blood pressure
  - Pediatric blood pressure norms are height based
- Impaired fasting glucose concentration
  - Some adolescents have transient insulin resistance during puberty
- Increased waist circumference
  - No standardization for diagnosing central obesity

- Metabolic abnormalities in children with metabolic syndrome are relatively moderate
### Table 1: Definitions of Pediatric Metabolic Syndrome in the Literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>Reference</th>
<th>Definition 1</th>
<th>Definition 2</th>
<th>Definition 3</th>
<th>Definition 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook et al.</td>
<td>Arch Pediatr Adolesc Med. 2003;157:821-827</td>
<td>Fasting glucose ≥110 mg/dL</td>
<td>Fasting glucose ≥6.1 mmol/L (≥110 mg/dL)</td>
<td>Impaired glucose tolerance (ADA criterion)</td>
<td>Impaired glucose tolerance (ADA criterion)</td>
</tr>
<tr>
<td>de Ferranti et al.</td>
<td>Circulation. 2004;110:2494-2497</td>
<td>WC ≥90th percentile (age and sex specific, NHANES III)</td>
<td>WC ≥75th percentile (age and sex specific, NHANES III)</td>
<td>BMI ≥ z-score ≥ 2.0 (age and sex specific)</td>
<td>WC ≥90th percentile (age and sex specific, NHANES III)</td>
</tr>
<tr>
<td>Cruz et al.</td>
<td>J Clin Endocrinol Metab. 2004;89:108-113</td>
<td>Triglycerides ≥110 mg/dL (age specific, NCEP)</td>
<td>Triglycerides ≥110 mg/dL (≥160 mg/dL)</td>
<td>Triglycerides ≥90th percentile (age and sex specific, NHANES III)</td>
<td>Triglycerides ≥90th percentile (age specific, NCEP)</td>
</tr>
<tr>
<td>Weiss et al.</td>
<td>N Engl J Med. 2004;350:2362-2374</td>
<td>HDL-C ≤40 mg/dL (all ages/sexes, NCEP)</td>
<td>HDL-C &lt;1.3 mmol/L (&lt;50 mg/dL)</td>
<td>HDL-C ≤10th percentile (age and sex specific, NHANES III)</td>
<td>HDL-C ≤5th percentile (age and sex specific, NGHS)</td>
</tr>
<tr>
<td>Ford et al.</td>
<td>Diabetes Care. 2005;28:876-881</td>
<td>Blood pressure ≥90th percentile (age, sex, and height specific)</td>
<td>Blood pressure &gt;90th percentile (age, sex, and height specific, NHBPFP)</td>
<td>Blood pressure ≥90th percentile (age, sex, and height specific, NCEP)</td>
<td>Blood pressure ≥90th percentile (age, sex, and height specific, NHBPFP)</td>
</tr>
</tbody>
</table>

**Three or more of the following:**

1. Fasting glucose ≥110 mg/dL
2. WC ≥90th percentile (age and sex specific, NHANES III)
3. Triglycerides ≥110 mg/dL (age specific, NCEP)
4. HDL-C ≤40 mg/dL (all ages/sexes, NCEP)
5. Blood pressure ≥90th percentile (age, sex, and height specific, NHBPFP)

**Abbreviations:** ADA, American Diabetes Association; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; NGHS, National Heart, Lung, and Blood Institute Growth and Health Study; NHANES, National Health and Nutrition Examination Survey; NHBPFP, National High Blood Pressure Education Program; WC, waist circumference.

<table>
<thead>
<tr>
<th>AGE GROUP (YEARS)</th>
<th>OBESITY* (WC)</th>
<th>TRIGLYCERIDES</th>
<th>HDL-C</th>
<th>BLOOD PRESSURE</th>
<th>GLUCOSE (MMOL/L) OR KNOWN T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-&lt;10</td>
<td>≥90th percentile</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension, and/or obesity.</td>
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<tr>
<td>10-&lt;16 metabolic syndrome</td>
<td>≥90th percentile or adult cutoff if lower</td>
<td>≥1.7 mmol/L (≥150 mg/dL)</td>
<td>&lt;1.03 mmol/L (&lt;40 mg/dL)</td>
<td>Systolic ≥130/ diastolic ≥85 mm Hg</td>
<td>≥5.6 mmol/L (100 mg/dL)</td>
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<tr>
<td>16+ metabolic syndrome</td>
<td>Use existing IDF criteria for adults, i.e:</td>
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<td>Central obesity (defined as WC ≥94 cm for Euroid men and ≥80 cm for Euroid women, with ethnicity specific values for other groups*) plus any 2 of the following 4 factors:</td>
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<tr>
<td></td>
<td>• Raised triglycerides: ≥1.7 mmol/L (≥150 mg/dL)</td>
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<tr>
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<td>• Reduced HDL-C: &lt;1.03 mmol/L (&lt;40 mg/dL) in males and &lt;1.29 mmol/L (&lt;50 mg/dL) in females, or specific treatment for these lipid abnormalities</td>
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<td>• Raised BP: systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension</td>
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<td></td>
<td>• Impaired fasting glycemia (IFG): fasting plasma glucose (FPG) ≥5.6 mmol/L (≥100 mg/dL), or previously diagnosed T2DM</td>
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</tbody>
</table>

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WC, waist circumference.
*The IDF Consensus group recognizes that there are ethnic, gender, and age differences, but research is still needed on outcomes to establish risk.


- MI, stroke, peripheral arterial disease, ruptured AA result from life long accumulation of atherosclerosis
- Lipid deposits in the vascular intima are found in youth and are reversible in initial stages
- Children with markedly elevated LDL, HTN, Type 1 DM and family history of MI have increased carotid intima-media thickness and / or endothelial dysfunction
- LVH at levels associated with increased mortality in adults has been found in children with severe obesity

- Height, Weight, BMI, Blood pressure, update CV risk family hx
- For children ≥ 10 yrs with BMI ≥ 85th percentile: lipid panel, and if other risk factors: fasting glucose and LFTs every 2 years, and more often if abnormal
- For children ≥ 10 yrs with BMI ≥ 95% percentile: lipid panel, and fasting glucose and LFTs every 2 years regardless of additional risk factors
- Skinfold thickness measurements and waist circumference measurements are not recommended
Comorbidities: NAFLD and NASH

- Most common liver disease in the US
- Male > Female
- Hispanic, White, Asian >> African American
  - Hispanic population is at 4 fold higher risk than other adolescents
- OSA
- Type 2 DM

- Two hit theory: first insulin resistance, increased free fatty acids, fat accumulation in the liver; second hit with oxidative stress – cytochrome polymorphisms (genetic predisposition) >> steatohepatitis
2016 NASPGHAN Guidelines

• Screen all obese children with BMI ≥ 95%ile and overweight children with risk factors: central adiposity, insulin resistance, pre-DM or DM, dyslipidemia, OSA, Family Hx of NAFLD or NASH

• Screen with ALT: Normal is <22 for girls and <26 for boys

• If ALT is ↑ for > 3 months and ALT ≥ 44 for girls or ≥ 50 for boys then refer to Hepatology

• If ALT > 80 then refer to Hepatology urgently as NASH is more common

• If normal, then repeat every 2-3 yrs if no major changes, sooner if rapid weight gain or new medical problem (OSA, DM)

• US is not recommended as a screening tool for NAFLD: liver biopsy
Comorbidities: Obstructive Sleep Apnea

• As many as 50% of severely obese teens have OSA
• Screen by asking parents about snoring with pauses in breathing, restless sleep, ask teens about daytime sleepiness
• Tonsilar hypertrophy
• Associated with poor attention, poor academic performance and enuresis
• RVH and pulmonary HTN
• Managing OSA with CPAP or tonsillectomy resulted in improvement in total chol (mean change -11 mg/dL, p<0.001) and LDL (mean change -8.8 mg/dL, p=0.021)

Amini et al, 2017
Comorbidities: Hypertension

- 13% of overweight children have elevated systolic blood pressure and about 9% have elevated diastolic blood pressure
- Use correct size BP cuff, correct position for taking blood pressure
New: Aug 2017
Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents
*Pediatrics*
Flynn JT et al
### For Children Aged 1–13 y

<table>
<thead>
<tr>
<th>Normal BP: &lt;90th percentile</th>
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</thead>
<tbody>
<tr>
<td>Elevated BP: ≥90th percentile to &lt;95th percentile or 120/80 mm Hg to &lt;95th percentile (whichever is lower)</td>
</tr>
<tr>
<td>Stage 1 HTN: ≥95th percentile to &lt;95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)</td>
</tr>
<tr>
<td>Stage 2 HTN: ≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg (whichever is lower)</td>
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</tbody>
</table>

### For Children Aged ≥13 y

<table>
<thead>
<tr>
<th>Normal BP: &lt;120/&lt;80 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated BP: 120/&lt;80 to 129/&lt;80 mm Hg</td>
</tr>
<tr>
<td>Stage 1 HTN: 130/80 to 139/89 mm Hg</td>
</tr>
<tr>
<td>Stage 2 HTN: ≥140/90</td>
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</table>

ABPM should be performed for confirmation of HTN in children and adolescents with office BP measurements in the elevated BP category for 1 year or more or with stage 1 HTN over 3 clinic visits.

Children and adolescents ≥6 y of age do not require an extensive evaluation for secondary causes of HTN if they have a positive family history of HTN, are overweight or obese, and/or do not have history or physical examination findings suggestive of a secondary cause of HTN.

Echocardiography should be performed at the time of consideration of pharmacologic treatment of HTN.
<table>
<thead>
<tr>
<th>BP reading</th>
<th>Screening/schedule</th>
<th>Diet and exercise counseling</th>
<th>Check bp in upper + lower extremities</th>
<th>Ambulatory BP Measurement</th>
<th>Lab work to exclude 2° HTN</th>
<th>Initiate treatment</th>
<th>Refer to specialist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &lt;120/&lt;80</td>
<td>Annual</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Elevated BP</td>
<td>Initial</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120/&lt;80 to 129/&lt;80</td>
<td>2\textsuperscript{nd} meas. after 6 mos</td>
<td>X, X</td>
<td>_</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>3\textsuperscript{rd} meas. after 6 mos.</td>
<td>X</td>
<td>_</td>
<td>X</td>
<td>X</td>
<td>_</td>
<td>X</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>Initial</td>
<td>X</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>130/80 to 139/89</td>
<td>2\textsuperscript{nd} meas. after 1-2 wk</td>
<td>X, X</td>
<td>_</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3\textsuperscript{rd} meas. after 3 mos.</td>
<td>X</td>
<td>_</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>Initial</td>
<td>X, X</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>≥140/90</td>
<td>2\textsuperscript{nd} meas. repeat and refer</td>
<td>X</td>
<td>_</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>w/in 1 week</td>
</tr>
</tbody>
</table>
Comorbidities: Type 2 DM

- Type 2 DM prevalence is 0.4-1% among obese youth, and has been increasing
- American Indian > Black > Hispanic >> Asian > Non-Hispanic White
- Many adolescents with T2DM are asymptomatic
- Screening for youth ≥10 yrs or at puberty, when BMI ≥ 85%ile, q 2 yrs
- Fasting glucose (≥126 mg/dL for DM and ≥100 for preDM) or HbA1c (≥5.7 mg/dL)
- Management is with diet and exercise with or without Metformin
Comorbidities: Polycystic Ovarian Syndrome

- 2015 Pediatric Endocrine Society: menstrual bleeding patterns abnormal for age, persisting for 1-2 years with evidence of hyperandrogenism (lab data is better than clinical assessment)
- Exclude thyroid disease, T2DM, prolactinoma, late-onset CAH, POI
- Management strategies include weight loss in overweight patients, Metformin, hormonal contraceptives for menstrual regulation, preventing endometrial hyperplasia, acne and hirsutism
CDC BMI (2000) growth chart, girls aged 2 to 20 years.

BMI for age Percentiles (Girls, 2 to 20)

Source: Centers for Disease Control and Prevention (CDC)

Alka K. Gulati et al. Pediatrics 2012;130:1136-1140

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What they don’t know might help?

• National Longitudinal Study of Adolescent to Adult Health data (N=2738):
  • Youth (male and female) who were overweight or obese but who perceived themselves to be normal weight had lower rates of weight gain from adolescence to adulthood over a 12 year period (adjusted for baseline BMI and SES)
  • Young women had lower blood pressure as young adults if they had perceived that they were normal weight (- 4.3 mm Hg, p=0.002 )

• Project EAT:
  • Better body satisfaction (adjusted for BMI and SES) predicted less weight gain over 5 years (N=376 female adolescents BMI >85%ile, p<0.01)
  • Poor body satisfaction predicted larger increase in BMI, and also less physical activity and more unhealthy eating and weight control behaviors 5 years later
Effects of “weight talk”

- **Project EAT**
  - Parental encouragement of dieting is associated with overweight youth remaining overweight 5 years later in boys (OR: 3.54, p = .07) and girls OR: 2.98, p = .032) N=170 parent-teen dyads
  - Parents who talk to teens about their weight are more likely to have kids that engage in disordered weight control behaviors compared with parents who talk only about healthy eating behaviors (N=821 overweight and obese teens)

- **NHLBI Growth and Health Study:**
  - Girls labelled as “too fat” by a parent, sibling, peers, teachers or other family members are more likely to be obese as young adult (N=849, OR 1.66, adjusted for baseline BMI, SES)
Atypical Anorexia Nervosa
What can we do to help without hurting?
Healthy lifestyle changes

• Sleep
• Screen time
• Physical activity
• Limiting sugary beverages
• Limit fast food and eating from restaurants
• Eating fruits and vegetables
• Meal and snack planning
• Managing emotions and stress
Medication options

• Orlistat: only FDA approved option for long-term treatment of obesity
  • FDA approved for youth 12 yrs and older
  • Effective for preventing weight gain in conjunction with diet modification and exercise
  • 120 mg q 8 hr dose may result in 0.4-1 BMI unit weight loss over 6 months
• Sympathomimetics: Phentirmine, Diethylproprion approved for ≥16 and Benzphetamine and phendimetrazine for ≥12 years
  • Short term use, need to assess weight loss at 2 months and discontinue if lack of response
  • Patients require close follow up, side effects and risk of abuse are limiting
  • Loss of weight caused by decreased appetite, and pt often regains after d/c
Metformin

• Works primarily by reducing blood sugar
• Start with 500 mg with dinner and titrate up to 1000 mg BID as tolerated
• Common side effects include GI discomfort
• Check liver and kidney function prior to initiation
• Discuss skipping Metformin if risk for dehydration (vomiting, diarrhea, avoid use with alcohol) for risk for lactic acidosis
• Expect modest result: up to 4.23 kg over 6 months in pediatric population
### Best practice updates for pediatric/adolescent weight loss surgery.
Pratt et al. Obesity 2009

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;35</td>
<td>Serious: Type 2 DM, mod/severe OSA, pseudotumor cerebri, severe steatohepatitis</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Other: mild OSA, hypertension, insulin resistance, glucose intolerance, dyslipidemia, impaired quality of life</td>
</tr>
</tbody>
</table>

**Eligibility Criteria**

- **Tanner Stage**
  - IV or V (unless severe comorbidities indicate WLS sooner)
- **Skeletal Maturity**
  - Completed ≥ 95% expected height (for diversional or malabsorptive procedures incl RYGB)
- **Lifestyle Changes**
  - Demonstrates ability to understand what dietary and physical activity changes will be required for optimal postoperative outcomes
- **Psychological**
  - Evidence for appropriate social support without evidence of abuse or neglect
  - If psychiatric condition (depression, anxiety, BED) is present, it is under treatment
  - Evidence that the family and patient have ability and motivation to comply with recommended treatments pre- and postoperatively, including consistent use of micronutrient supplements. Evidence may include a history of reliable attendance at office visits for weight management and compliance with other medical needs.

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*a* All criteria must be fulfilled
SLOW DOWN  KEEP CALM  BE POSITIVE  TAKE IT EASY
UNPLUG  ENJOY LIFE  HAVE FUN  BREATHE
RELAX  GO OUTSIDE  MEDITATE